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Practice Advisory on the Appropriate Use of NSAIDs in Primary Care

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Abstract: Cyclo-oxygenase (COX)-2 selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are important in managing acute and chronic pain secondary to inflammation. As a greater understanding of the risks of gastrointestinal (GI), cardiovascular (CV) and renal events with NSAIDs use has emerged, guidelines have evolved to reflect differences in risks among NSAIDs. Updated guidelines have yet to reflect new evidence from recent trials which showed similar CV event rates with celecoxib compared to naproxen and ibuprofen, and significantly better GI tolerability for celecoxib. This practice advisory paper aims to present consensus statements and associated guidance regarding appropriate NSAID use based on a review of current evidence by a multidisciplinary group of expert clinicians. This paper is especially intended to guide primary care practitioners within Asia in the appropriate use of NSAIDs in primary care. Following a literature review, group members used a modified Delphi consensus process to determine agreement with selected recommendations. Agreement with a statement by 75% of total voting members was defined a priori as consensus. For low GI risk patients, any nonselective NSAID plus proton pump inhibitor (PPI) or celecoxib alone is acceptable treatment when CV risk is low; for high CV risk patients, low-dose celecoxib or naproxen plus PPI is appropriate. For high GI risk patients, celecoxib plus PPI is acceptable for low CV risk patients; low-dose celecoxib plus PPI is appropriate for high CV risk patients, with the alternative to avoid NSAIDs and consider opioids instead. Appropriate NSAID prescription assumes that the patient has normal renal function at commencement, with ongoing monitoring recommended. In conclusion, appropriate NSAID use requires consideration of all risks.

Keywords: cardiovascular risk, COX-2 selective inhibitors, gastrointestinal risk, nonsteroidal anti-inflammatory drugs, osteoarthritis, inflammation

Introduction

Chronic pain is one of the most common causes of disability worldwide and is routinely observed in the primary care setting.¹ The presence of inflammation is a key underlying mechanism of chronic pain and is a key contributor to the pathophysiology of rheumatic conditions, including rheumatoid arthritis, spondyloarthropathies and osteoarthritis (OA).^{2,3} These conditions have a major impact in terms of health burden and adverse effects on quality of life in affected people throughout the world, and especially in developing countries including those in Asia.⁴ Moreover, with an aging population, the prevalence of chronic pain will continue to rise and the role of the primary care practitioner (PCP) as care providers and prescribers of analgesic medications will become more important.

Consistent with an inflammatory mechanism, common analgesics used in the management of chronic pain include paracetamol and nonsteroidal anti-inflammatory

drugs (NSAIDs). Although considered a first-line analgesic, paracetamol provides limited short-term clinical benefit and is associated with side effects of hepatotoxicity and hypertension.^{5–8} Opioids are also prescribed in cases requiring step-up pain relief and when pain is thought to have a non-inflammatory etiology. In addition to side effects of nausea, vomiting and constipation, the over-prescription of opioids has led to a sharp increase in the prevalence of opioid addiction and epidemic levels of associated morbidity and mortality.⁹ NSAIDs, which in terms of prescribing patterns are often the bridge between paracetamol and opioids, are commonly used to treat inflammation through their actions on the cyclo-oxygenase (COX) enzyme, which is found in two distinct isoforms, COX-1 and COX-2.^{10,11} Whereas inhibition of COX-2 confers relief from inflammation and pain, COX-1 inhibition commonly leads to gastrointestinal (GI) and renal side effects.^{12,13}

NSAIDs may be either nonselective in that they inhibit both COX-1 and COX-2, or selective in that they only inhibit COX-2 (coxibs).¹³ The COX-2 selective NSAIDs, celecoxib and rofecoxib, were the first members of the new class to be introduced in the 1990s in an attempt to reduce GI side effects associated with NSAID use. However, rofecoxib was withdrawn from the market in 2004 due to its association with an increased incidence of cardiovascular (CV) adverse events.^{14,15} Research published in the decade after rofecoxib's market withdrawal attempted to further elucidate the safety of NSAIDs, with an emphasis on determining whether the CV concerns associated with rofecoxib use were a class effect of coxibs. CV risk not only varied among different COX-2 selective NSAIDs (the CV risk was higher for rofecoxib than celecoxib), but when considered overall, serious CV events for nonselective NSAIDs compared with COX-2 selective NSAIDs occurred at approximately equal rates.¹⁶ In some studies, elevated risk was associated with certain nonselective NSAIDs, such as out-of-hospital cardiac arrest and major adverse cardiac events (MACE) in the case of diclofenac.^{17,18} Thus, COX-selectivity is not binary, with the COX-2 isoform alone not defining the CV risk of an NSAID.¹⁹ Moreover, NSAIDs have been shown to have differential effects on blood pressure (BP), with rofecoxib, etoricoxib and the nonselective NSAID ibuprofen demonstrating greater increases in systolic BP than celecoxib.^{20–22} This has obvious implications because hypertension is a known risk factor for CV adverse events. Finally, recent data from the PRECISION trial have shown the noninferiority of celecoxib when compared to ibuprofen and

naproxen with regard to CV safety.²³ Ibuprofen and naproxen, in contrast, had greater GI and renal toxicity.

Among PCPs, there is often a lack of awareness of the CV, GI and renal risks associated with the use of NSAIDs.²⁴ As a result, PCPs may not routinely identify patient risk factors before prescribing NSAIDs. Conversely, there may be an overestimation of NSAID-associated risk, leading to prescription of suboptimal doses for pain relief. In addition, patients are largely unaware of the potential harms associated with nonselective NSAID use when taking over-the-counter products.²⁵ Moreover, updated practice recommendations are needed to reflect data from recent trials. At present, the only available COX-2 selective inhibitors are celecoxib, etoricoxib and parecoxib. Celecoxib and etoricoxib are available as oral preparations, whereas parecoxib is the injectable prodrug of valdecoxib. Rofecoxib and valdecoxib have been withdrawn from market due to concerns over CV safety and serious dermatological reactions, respectively; lumiracoxib has been withdrawn because of risk of liver toxicity.^{26,27} The aim of this practice advisory is to summarize the current evidence regarding NSAID use and provide updated guidance to PCPs on prescription of oral NSAIDs, with an emphasis on CV, GI and renal safety.

Materials and Methods

In November 2018, an expert meeting was convened in Kuala Lumpur, Malaysia involving a multidisciplinary group of clinicians to discuss the appropriate use of NSAIDs. The objectives of the meeting were to review current clinical data for NSAIDs including data for PRECISION and other international studies on NSAIDs, and identify knowledge gaps regarding NSAID use in Asia. Members of the group included specialists in pain management, orthopaedic surgery, neurology, cardiology, gastroenterology, nephrology and rheumatology from Indonesia (Rizaldy Pinzon, Sumariyono Sarmidi), Japan (Ken Nakata, Shuichi Tsuruoka), Korea (Ji Hyeon Ju), Malaysia (Mary Cardosa, Ozlan Kamil, Sabarul Mokhtar), Philippines (Sandra Navarra), Singapore (Kok Yuen Ho, Heng Boon Yim), Thailand (Sumapa Chaiamnuay), Vietnam (Ho Huynh Quang Tri, Nguyen Van Hung), and the United Kingdom (Ernest Choy).

At the meeting, the group agreed to develop a practice advisory document to guide Asian PCPs in the appropriate use of NSAIDs in the primary care setting. The group selected pertinent topics to include in two succeeding online meetings. Members of the group were assigned to

individual topics, with group representatives conducting a MEDLINE search for relevant articles dated from January 1, 2000, and limited to English language articles. Relevant articles were selected and reviewed, and assigned members subsequently developed proposals for ten clinically relevant consensus statements relating to NSAID use to represent the group's clinical practice recommendations for Asian PCPs. The consensus process was a modification of the Delphi method, with members of the voting group asked to rate their agreement with each recommendation on a 5-point Likert scale (ie, 5, strongly agree; 4, agree; 3, neither agree nor disagree; 2, disagree; 1, strongly disagree). Agreement by 75% of total voting members based on the proportion of members who either strongly agreed or agreed with a statement was defined a priori as consensus achieved for a statement. Consensus was achieved for all statements in the first voting round. Consequently, members of the group were not required to reconvene as originally planned to discuss modifications of the consensus statements based on feedback from the first voting round.

Current Evidence

Beyond COX selectivity, there are marked differences in the molecular and chemical properties of individual drugs even when comparing within the respective subclasses (Table 1).^{28–31} For example, ibuprofen and naproxen are both derivatives of propionic acid, whereas diclofenac is a benzeneacetic derivative; celecoxib and valdecoxib both have a sulfonamide group, whereas etoricoxib and rofecoxib have a sulfonyl group.³² Although all NSAIDs are acidic compounds, the acid dissociation constant (pKa) varies from 9.7 for celecoxib to 4.0 for diclofenac.³¹ Compared with COX-2 selective NSAIDs, the nonselective NSAIDs are weak acids. Among the COX-2 selective NSAIDs, selectivity for the COX-2 enzyme varies considerably, with greater selectivity for the discontinued drugs lumiracoxib, rofecoxib and valdecoxib, as well as etoricoxib, and lower selectivity for celecoxib.¹⁹

These differences in molecular structure and chemistry naturally confer different pharmacologic properties on the individual drugs. The weak acidity of nonselective NSAIDs confers detergent properties on account of their lipophilicity. This allows interactions with phospholipids of the brush border, increasing cell permeability, and promoting damage to the epithelial lining of the gut.^{31,33} Weaker acidity may also be associated with the loss of cellular integrity due to pH-dependent effects that involve

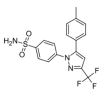


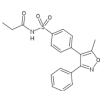
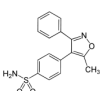
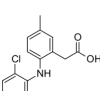
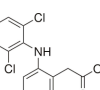
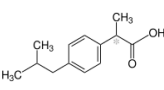
NSAID-mediated uncoupling of oxidative phosphorylation and reduced intracellular ATP production.³¹ The sulfonyl group associated with rofecoxib, but not the sulfonamide group of celecoxib or the chemical structures of other nonselective NSAIDs, has been shown to increase the susceptibility of low-density lipoprotein (LDL)-cholesterol and related lipids to oxidative modification independent of COX-2 inhibition.³⁴ This nonenzymatic oxidation of LDL-cholesterol contributes to atherogenesis and CV disease.

Gastrointestinal Risks

Endoscopic evidence of mucosal injury in the upper GI tract is common with chronic use of NSAIDs, affecting as many as 70% of chronic users compared with 10% of people not taking NSAIDs.³⁵ In one meta-analysis, all NSAID regimens including nonselective and COX-2 selective agents were shown to increase the risk of upper GI complications.³⁶ Although ulceration and related bleeding are much less common events, the mechanism of NSAID-mediated GI injury is the same. Previously, this was explained in terms of COX-1-dependent depletion of prostaglandins and the subsequent impairment of the protective role of prostaglandins in stimulating the synthesis and secretion of mucus and bicarbonate, as well as promoting epithelial proliferation.³⁷ However, it is now apparent that inhibition of both COX-1 and COX-2 must occur to spur gastric ulceration, with the reduced impact of COX-2 selective NSAIDs on GI toxicity thus explained by the absence of dual COX inhibition rather than any COX-1 sparing effects.^{14,37–39}

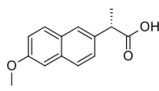
Factors that increase the risk of GI toxicity with NSAID use include older age, history of peptic ulcer disease/complications, *Helicobacter pylori* infection, high-dose NSAID use, and concomitant use of certain drugs, including corticosteroids, anticoagulants and antiplatelet agents. Age-related risk reflects the tendency of chronic pain medication use among an older age cohort (≥60 years) with an increased likelihood of comorbidities and potential complications associated with polypharmacy.^{30,31} A pooled analysis of 21 randomized controlled trials (RCTs) showed that among elderly arthritis patients, the use of celecoxib reduced the incidence of GI adverse events including abdominal pain, constipation, diarrhea, dyspepsia, flatulence and nausea compared with naproxen, ibuprofen or diclofenac.⁴⁰ In another meta-analysis of more than 50,000 patients enrolled in 52 RCTs, when compared with nonselective NSAIDs, celecoxib was associated with a significantly lower risk of all clinically significant GI events throughout the entire GI tract.⁴¹ In the

Table 1 Molecular and Chemical Properties of Cyclo-Oxygenase (COX)-2 Selective and Nonselective Nonsteroidal Anti-Inflammatory Drugs

Compound	Status	Classification	Chemical Structure	Acidity (pK)	COX-1/ COX-2 IC ₅₀ Ratio*	Clinical Implications
Celecoxib	Licensed in all markets	COX-2-selective, sulfonamide structure		9.7 (low)	30 (moderate)	Low intestinal permeability, no effect on lipid-oxidation susceptibility
Rofecoxib	Withdrawn from market	COX-2-selective, methylsulfone structure		8.6 (intermediate)	272 (high)	Intermediate intestinal permeability, increased lipid-oxidation susceptibility
Etoricoxib	Not FDA approved, licensed in EU	COX-2-selective, methylsulfone structure		4.5 (moderate)	344 (very high)	Moderate intestinal permeability, heightened lipid-oxidation susceptibility
Parecoxib	FDA withdrawn, licensed in EU	COX-2-selective, sulfonamide structure		6.7 (moderate)	60 (intermediate)	increased lipid-oxidation susceptibility
Valdecoxib	Withdrawn from market	COX-2-selective, sulfonamide structure		9.8 (low)	60 (intermediate)	Low intestinal permeability, increased lipid-oxidation susceptibility
Lumiracoxib	Withdrawn from market	COX-2-selective, arylalkanoic acid structure		4.7 (moderate)	400 (highest)	Moderate intestinal permeability, heightened lipid-oxidation susceptibility
Diclofenac	Licensed in all markets	Acetic acid derivative		4.0 (moderate)	12 (low)	Moderate intestinal permeability, no effect on lipid-oxidation susceptibility
Ibuprofen	Licensed in all markets	Propionic acid derivative		5.2 (moderate)	≤1 (very low)	Moderate intestinal permeability, no effect on lipid-oxidation susceptibility

(Continued)

Table 1 (Continued).

Compound	Status	Classification	Chemical Structure	Acidity (pK)	COX-1/COX-2 IC ₅₀ Ratio*	Clinical Implications
Naproxen	Licensed in all markets	Propionic acid derivative		4.2 (moderate)	≤1 (very low)	Moderate intestinal permeability, no effect on lipid-oxidation susceptibility

Notes: Table derived from information presented in references.^{28–31} *COX-2 selectivity based on the IC₈₀ (80% inhibitory concentration) of COX-2 relative to COX-1 in human whole blood assays.

Abbreviations: COX-1, cyclo-oxygenase-1; COX-2, cyclo-oxygenase-2; EU, European Union; FDA, US Food and Drug Administration.

MEDAL program, which evaluated the gastrointestinal safety of etoricoxib compared with diclofenac in almost 35,000 patients with OA and rheumatoid arthritis (RA), etoricoxib was associated with significantly fewer upper GI events than diclofenac.⁴² However, the difference between etoricoxib and diclofenac was explained by a reduction in uncomplicated events in the etoricoxib arm, but not in the more serious complicated events.

In the context of all NSAID therapy, *H. pylori* infection increases the risk of ulceration and bleeding, and its eradication prior to commencing long-term antiplatelet therapy is recommended to reduce GI risk.³¹ The risk of GI toxicity increases at high NSAID doses,³⁶ but even at standard doses the risks are not negligible: the CLASS study showed that the risk of upper GI ulceration was higher for standard doses of ibuprofen or diclofenac compared with celecoxib administered at doses greater than those indicated clinically.³⁸ In addition to antiplatelet therapy, GI risk is increased with concomitant use of corticosteroids and selective serotonin reuptake inhibitors (SSRIs).^{37,43}

Appropriate assessment of patient GI risk includes age, prior GI ulceration or bleeding, use of gastroprotective agents, and use of corticosteroids and other medications.^{44,45} In addition to assessment, the risk of GI toxicity with NSAID use can be mitigated through regular monitoring to facilitate the early detection of injury and appropriate treatment. Hemoglobin levels can be used as an indicator of GI injury, with low hemoglobin and hematocrit attributable to blood loss in the absence of other potential causes.³⁰ A drop in hemoglobin of ≥2 g/dL is a well-recognized surrogate endpoint for investigating NSAID-associated GI toxicity in clinical trials.

One strategy used to minimize the risk of GI complications involves the coadministration of NSAIDs with a

proton pump inhibitor (PPI).⁴⁶ Such coadministration is generally regarded as safe and is recommended in guidelines. However, recent evidence challenging this view suggests that in addition to the adverse effects of PPIs, their coadministration with NSAIDs may potentiate the GI risks of the latter.³⁰ In particular, PPIs have been shown to alter gut microbiome composition leading to the risk of bacterial overgrowth and contributing to a low-grade, chronic inflammation that can exacerbate NSAID-induced mucosal injury of the small bowel.³⁰ In some patients at least, the use of PPIs may increase the risk of bone fractures, *Clostridium difficile* and other enteric infections, and gastric cancer.^{47,48} Extrapolation of results of the CONDOR trial and related studies also suggest that PPI prophylaxis may be unnecessary in some long-term NSAID users.^{39,49,50} The CONDOR trial evaluated celecoxib compared with diclofenac plus omeprazole in patients with OA and RA. The findings showed that the risk of a clinically significant upper or lower GI event was lower in patients treated with a COX-2 selective NSAID compared with a nonselective NSAID plus PPI.⁵⁰ In patients at high risk of GI bleeding, concomitant PPI use remains an appropriate strategy for managing GI risk, particularly when prescribed in accordance with any risk factors.³⁷ In the MEDAL program, the reduction in uncomplicated GI events with etoricoxib compared with diclofenac was maintained in patients treated with PPIs.⁴²

Preventative strategies for GI toxicity may be used both for primary and secondary prevention, and include the eradication of *H. pylori* and use of PPIs as already discussed, together with the use of enteric-coated NSAIDs and high-dose H₂ receptor antagonists (H₂RAs).^{37,51} Evidence suggests that enteric-coating of NSAIDs does not reduce the incidence of upper GI complications compared with other formulations, but may shift the site of

injury to more distal regions of the gut.³⁰ The use of PPI prophylaxis is likely to be more effective than the use of H2RAs, with the latter protective at high doses, but ineffective at reducing the risk of gastric ulcers at lower doses.⁵² Although the use of PPI prophylaxis can improve GI tolerability during chronic NSAID administration and may also prevent upper GI complications, video endoscopy has shown that the risk of small bowel lesions remains even in healthy subjects.³⁹ Furthermore, the beneficial effects of PPIs on upper GI complications do not extend to the lower GI tract, with PPI use unable to prevent NSAID or aspirin-associated lower GI bleeding.⁵³ Another gastroprotective strategy involves the use of misoprostol, which is effective at preventing upper GI bleeding in high-risk patients and may be appropriate in case of intolerance to PPIs.⁵⁴ There is also support for *H. pylori* eradication particularly in Asia where the prevalence is high,^{55–57} but available data suggest that *H. pylori* eradication in infected patients is at best equivalent to PPIs in preventing GI complications and may even be inferior.³⁰

Cardiovascular Risks

As the previous experience with rofecoxib demonstrates, there is also the potential for adverse CV events with NSAIDs. Already discussed, the proatherogenic potential of rofecoxib which was shown in the VIGOR trial to manifest as an increased risk of CV events compared with placebo^{14,15,58,59} may arise as a consequence of non-enzymatic oxidation.³⁴ However, experimental evidence that COX-2 inhibition may contribute to a prothrombotic state has placed suspicion on COX-2 selective inhibitors in general.⁶⁰ In particular, by suppressing vasodilation and the anti-aggregation effects associated with prostacyclin production, and leaving COX-1-dependent platelet thromboxane (TX) A₂ synthesis unopposed, COX-2 selective inhibitors may increase platelet aggregation via prostacyclin blockade and thus promote thrombosis.^{58,61} COX-dependent inhibition of prostaglandin synthesis may also contribute to sodium and water retention, worsening heart failure, hypertension, and effects on the renal system.^{21,62} At a mechanistic level, there are differences among NSAIDs. For example, celecoxib but not rofecoxib reduces endothelial tissue-factor expression, a key initiator of the coagulation cascade, and may thus have a lower prothrombotic potential.^{61,63}

Considering CV safety, there is considerable evidence that different COX-2 selective inhibitors and non-selective NSAIDs have different CV safety profiles.^{18,23,64} For

example, the nonselective NSAID diclofenac presents significantly greater CV risk compared with ibuprofen, naproxen, paracetamol, and non-analgesic use.¹⁸ In the MEDAL study, the COX-2 selective NSAID etoricoxib was associated with a similar risk of thrombotic events to diclofenac,⁶⁵ while at moderate doses, celecoxib afforded similar CV safety to ibuprofen and naproxen.²³ Naproxen use compared with other NSAIDs has previously been associated with a protective effect against acute myocardial infarction (MI).⁶⁶ However, in meta-analyses, all NSAIDs including naproxen were associated with an increased risk of acute MI,⁶⁷ and most increased the risk of heart failure.³⁶ Real-world data also suggest a heightened CV risk with NSAID use.⁶⁴ Among the discontinued COX-2 selective inhibitors, the TARGET RCT showed in more than 18,000 patients with OA that lumiracoxib had similar CV safety to ibuprofen and naproxen, irrespective of aspirin use.⁶⁸ However, findings of a post hoc analysis of TARGET subsequently suggested that ibuprofen may confer an increased risk of both thrombotic events and congestive heart failure events compared with lumiracoxib among aspirin users at high CV risk.⁶⁹ In a subsequent meta-analysis of six trials, there were no significant differences in CV outcomes between lumiracoxib and placebo or other NSAIDs in patients with OA.⁷⁰ The APPROVe study compared rofecoxib with placebo in patients with a history of colorectal adenomas and showed an increase in the composite endpoint of nonfatal MI, nonfatal stroke and death from CV, hemorrhagic and unknown causes for patients receiving rofecoxib.⁷¹

The SCOT and PRECISION studies are useful in framing the evidence related to the CV safety of NSAIDs. SCOT enrolled patients aged 60 years and older with OA or RA and without established CV disease who were taking prescribed chronic nonselective NSAIDs.⁷² Switching to celecoxib resulted in a similar rate of CV events as continuing on prescribed nonselective NSAIDs; GI safety was improved with celecoxib, though more patients assigned to nonselective NSAIDs remained on treatment. PRECISION assessed the noninferiority of celecoxib compared with ibuprofen and naproxen with respect to the primary composite outcome of CV death, nonfatal MI or nonfatal stroke, also in patients with OA and RA.²³ At approved dosages (mean daily dose 209 mg), celecoxib was associated with a significantly lower risk of GI events whereas overall CV safety was similar for the three drugs. However, allocation to ibuprofen compared with celecoxib was associated with a significant increase

in systolic BP and a higher rate of new onset hypertension.²¹ Among patients with symptomatic arthritis who had at least a moderate CV risk, patients using naproxen or ibuprofen had a significantly higher risk of a major toxicity, including time to first occurrence of MACE, important GI events, renal events, and all-cause mortality.⁷³ Among non-selective NSAIDs, naproxen may be preferred over ibuprofen. In one study, ibuprofen and diclofenac were associated with an increased early risk of out-of-hospital cardiac arrest.¹⁷ Further, the use of ibuprofen in patients receiving aspirin as secondary prevention of MI may abrogate the benefits of aspirin.⁷⁴

The MEDAL program similarly showed differences between a nonselective and a COX-2 selective NSAID in terms of BP effects. However, unlike PRECISION whose findings favored celecoxib compared with ibuprofen, the use of etoricoxib in MEDAL was associated with significantly increased systolic BP compared with diclofenac.⁷⁵ A subsequent study concluded that baseline BP rather than the BP-elevating effects of etoricoxib explained the risk of thrombotic events.⁷⁶

Celecoxib may thus be associated with increased CV risk, but only at dosages that are substantially higher than recommended.⁷⁷ Indeed, greater risk of MI and MACE have been documented for higher doses of NSAIDs, with risk in the case of MI also greatest during the first month of use.^{64,67} Greater CV risk may also be associated with older age, and related concerns regarding comorbidities and polypharmacy.

Renal Risks

In addition to the GI and CV effects of NSAIDs, epidemiological and pathologic data also associate NSAID use with the potential for both acute and chronic kidney disease (CKD).^{78–84} Renal side effects which include sodium and water retention with edema, hyponatremia, hyperkalemia, and acute kidney injury may precipitate renal failure resulting in acute dialysis.^{62,85} Risk factors include older age, renal impairment, heart failure, liver disease, diabetes mellitus (DM), and concurrent prescription with antihypertensive drugs (eg, diuretics, renin-angiotensin system inhibitors).^{62,86,87} Again, mechanisms of NSAID-induced kidney damage relate to inhibition of prostaglandin synthesis and are dose- and duration-dependent.^{80,81} Low levels of COX-2 are constitutively expressed in the macula densa, with COX-2 inhibition leading to a reduction in renal blood flow and resulting functional impairment. NSAIDs may also accumulate in renal tubular cells during

secretion. While NSAID-induced sodium retention is COX-2-mediated, NSAID-induced reductions in glomerular filtration rate are mediated via COX-1.¹³

Consistent with the dual COX-1/COX-2-dependent mechanisms, which predict the possibility of differences in renal toxicity for different NSAIDs, there are limited data to suggest clinically relevant differences.^{84,88} In the MEDAL program, etoricoxib had a greater risk of renovascular adverse events than diclofenac.⁶⁵ In PRECISION, the risk of renal events was significantly lower with celecoxib compared with ibuprofen, and was similar for celecoxib compared with naproxen.²³ In a meta-analysis, NSAIDs with high COX-2 selectivity had a lower association with acute kidney injury (AKI) compared to NSAIDs with low COX-2 selectivity.⁸³ Overall, NSAIDs have a low but tangible risk in causing AKI, electrolyte imbalances and increased BP, but their role in progressive kidney disease is associated only with long-term use in high cumulative doses.⁷⁸ In patients with CKD, withdrawal of NSAID use is recommended by nephrology consensus groups, but initiation of alternatives such as opioids conveys different and no less important drug-related concerns.^{89,90} In a study conducted in China that included age- and sex-matched controls of NSAID users, long-term (≥ 48 months) use of NSAIDs was independently associated with reduced renal function.⁹¹ It is recommended that patients with risk factors for renal impairment have preventative strategies in place that include using the lowest effective NSAID dose for the shortest possible time, as well as monitoring renal function, fluid retention and electrolyte abnormalities.^{62,92} The concomitant use of NSAIDs and angiotensin converting enzyme (ACE) inhibitors should be avoided.

Practice Advisory Statement

Screening for CV, GI and Renal Risk Factors Prior to Initiating NSAID Therapy

Statement 1: Prior to initiating NSAID therapy for a patient, the following factors must be taken into consideration. (Level of agreement: strongly agree, 86%; agree, 14%; consensus, 100%).

Age, associated medical comorbidities, previous medical or surgical history, concomitant use of medications (particularly antiplatelet medications, anticoagulants, corticosteroids, ACE inhibitors and SSRIs), *H. pylori* infection, and BP monitoring should be taken into consideration before

initiating NSAID therapy. The use of aspirin increases bleeding risk even at low cardioprotective doses, with bleeding risk also increased when non-aspirin NSAIDs are combined with aspirin.⁹³ Furthermore, coadministration of aspirin and most other NSAIDs can lead to drug–drug interactions, which is based on competition for access to the acetylation site of platelet-expressed COX-1. Non-aspirin NSAIDs drive the reversible, transient inhibition of platelet aggregation, thus blocking aspirin's irreversible inhibition and potentially allowing clot formation. Although aspirin maintains its cardioprotective benefits in the presence of non-aspirin NSAIDs,⁹⁴ the combination of aspirin and ibuprofen has been shown to increase the risk of a CV event.^{95,96}

Several meta-analyses have reviewed the potential for SSRIs to cause upper GI bleeding. All have reported an increased risk of such bleeding when SSRIs are used alone and especially in combination with NSAIDs.^{97–100} Caution is advised when there is a need to administer both medication classes in combination.

As discussed, *H. pylori* infection has a high prevalence in Asian patients, which has important implications for potential GI risk. NSAID use and *H. pylori* infection are independent risk factors for GI complications,^{101,102} with synergism for the development of peptic ulcer and bleeding found when NSAIDs are used in patients with *H. pylori* infection. Conversely, peptic ulcer disease is rare in people who are negative for *H. pylori* infection.¹⁰¹ This provides a rationale for eradicating *H. pylori* in patients requiring chronic NSAID use. Moreover, eradication of *H. pylori* prior to the start of long-term NSAID use is associated with a reduced risk of ulcers and appears to be especially effective in NSAID drug-naïve patients.^{103–105} Patients requiring long-term treatment with NSAIDs and with epigastric pain or dyspepsia, or otherwise assessed as high GI risk, should be referred to a gastroenterologist for a detailed evaluation, including *H. pylori* testing and possible gastroscopy; those testing positive for *H. pylori* may be offered eradication therapy.

Statement 2: Consider taking a baseline complete blood count and renal function test (if not previously available) in the following patients. (Level of agreement: strongly agree, 64%; agree, 36%; consensus, 100%).

In patients with a history of renal impairment, congestive heart failure, elevated BP and/or type 2 diabetes mellitus, or the presence of unexplained anemia, consider

a complete blood count and assessment of renal function prior to initiating an NSAID.

Statement 3: Use NSAIDs with caution in the following high-risk patients. (Level of agreement: strongly agree, 79%; agree, 21%; consensus, 100%).

Patients at high risk of NSAID-associated adverse events may be stratified according to GI, CV and renal risk. Patients considered to be at high GI risk are those with age greater than 65 years, use of high-dose NSAIDs, history of peptic ulcer and related complications, and concurrent use of aspirin, anti-platelet therapy or anti-coagulant therapy (and especially patients receiving double anti-platelet therapy). Patients at high CV risk are those with a history of acute coronary syndrome or percutaneous/surgical coronary revascularization, stable angina and angiographic evidence of significant coronary artery stenosis, a history of stroke/transient ischemic attack, documented significant carotid artery stenosis, or congestive heart failure. Patients at high renal risk are those with age greater than 75 years, impaired renal function based on estimated glomerular filtration rate less than 60 mL/min, and concomitant administration of an antihypertensive from any of the diuretic, angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) classes. Analgesics such as paracetamol, tramadol or codeine may be used in place of NSAIDs if the risks of NSAID treatment outweigh the potential benefits. However, the efficacy, availability and potential adverse effects of these alternatives also need to be considered in any decision-making regarding appropriate analgesia.

Choice of NSAIDs

All oral nonselective NSAIDs and COX-2 selective inhibitors have analgesic effects of a similar magnitude, but differences may exist among individual drugs in terms of potential GI, CV, renal or liver toxicities.¹⁰⁶

Statement 4: The choice of NSAID should depend on patient risk profile, pathophysiology of the pain condition, duration of therapy, and efficacy/side effects of the drug. Level of agreement: strongly agree, 93%; agree, 7%; consensus, 100%).

Statement 5: The lowest effective dose and for the shortest duration, consistent with treatment goals,

remains the guiding principle. (Level of agreement: strongly agree, 100%; consensus, 100%).

Statement 6: Current GI protective therapies are generally adequate for protection of the upper GI tract of NSAID users. (Level of agreement: strongly agree, 21%; agree, 57%; consensus, 78%).

This statement was a point of contention among the group and represents a compromise from the original statement, which was formulated as: GI protective therapies are generally inadequate or inappropriate in NSAID users. Consensus was not formed for this statement, necessitating rephrasing of the statement to the above wording (Level of agreement: strongly agree, 21%; agree, 43%; consensus, 64% [not reached]). In line with the revision, the group agreed that GI protective therapies (eg, PPIs) benefit patients who require an NSAID and who have a moderate to high risk for upper GI complications.^{37,46,51,54} There is little or no evidence to support any protection against lower GI side effects.

Statement 7: COX-2 selective NSAIDs are superior to nonselective NSAIDs for preventing both upper and lower GI tract adverse events. (Level of agreement: strongly agree, 43%; agree, 57%; consensus, 100%).

CONDOR, a large RCT that compared upper and lower GI safety of celecoxib with that of diclofenac plus omeprazole in patients with OA and RA, was the first trial to show that GI risk throughout the GI tract was significantly reduced in patients treated with a COX-2 selective inhibitor compared with a nonselective NSAID.^{41,50} Along with the SUCCESS trial and the MEDAL program, which also showed superior upper GI safety for celecoxib and etoricoxib, respectively, compared with nonselective NSAIDs, these data support the statement that COX-2 selective NSAIDs are superior to nonselective NSAIDs in the prevention of GI adverse events.

Statement 8: Both nonselective NSAIDs and COX-2 selective NSAIDs may increase renal adverse effects. (Level of agreement: strongly agree, 36%; agree, 64%; consensus, 100%).

The findings of a meta-analysis showing that NSAIDs with high COX-2 selectivity (≥ 5 -fold) had a lower association with AKI than NSAIDs with lower (< 5 -fold) COX-2 selectivity

together with findings from PRECISION showing a lower risk of renal events with celecoxib compared with ibuprofen provide some evidence of differences in renal risk based on individual NSAID selection.^{23,83}

Statement 9: The treatment algorithm should consider the renal function, GI risk and CV risk profile of the patient. (Level of agreement: strongly agree, 79%; agree, 21%; consensus, 100%).

All NSAIDs have features that are useful to highlight from a safety perspective. Among the nonselective NSAIDs, although diclofenac has the least risk of GI side effects, it also has the highest risk of CV events while also associated with increased risk of hepatic impairment. Based on data from PRECISION, ibuprofen not only has a higher risk than celecoxib of GI side effects, but is also associated with a higher risk of new-onset hypertension.^{21,23,73} In addition, ibuprofen and diclofenac use carries a higher risk of cardiac arrest compared with celecoxib.¹⁷ Based on findings of the MEDAL study, etoricoxib has a comparable risk to diclofenac of thrombotic CV events but a higher risk of renovascular events.⁶⁵ Etoricoxib use is also associated with dose-related increases in risk of hypertension, edema and congestive heart failure.⁶⁵

In patients taking aspirin for secondary stroke or coronary thrombosis prevention, COX-2 selective NSAIDs are the drugs of choice due to the potential for COX-1-associated drug-drug interactions and, in particular, the known risks of combining aspirin with ibuprofen.⁹³ While previous guidelines have recommended that naproxen plus PPI or celecoxib plus PPI can be given in patients with high GI and high CV risk, for patients taking low-dose aspirin the use of celecoxib plus PPI is the better choice. As shown in PRECISION, celecoxib has better overall GI safety than ibuprofen or naproxen despite treatment with low-dose aspirin or corticosteroids.¹⁰⁷

Based on data from PRECISION, a toxicity risk score that predicts the one-year risk of major toxicity has been validated among NSAID users.¹⁰⁸ Major toxicity included MACE, AKI, significant GI events and mortality. In the derivation cohort from PRECISION, significant variables that predicted increased risk of a major toxicity were age, male sex, history of CV disease, hypertension, DM, tobacco use, statin use, elevated serum creatinine, hematocrit level, and type of arthritis. Based on an individual patient's calculated risk score, the patient can be classified into one of three categories, including low risk ($< 1\%$), moderate risk ($1-4\%$) and high risk ($\geq 4\%$).

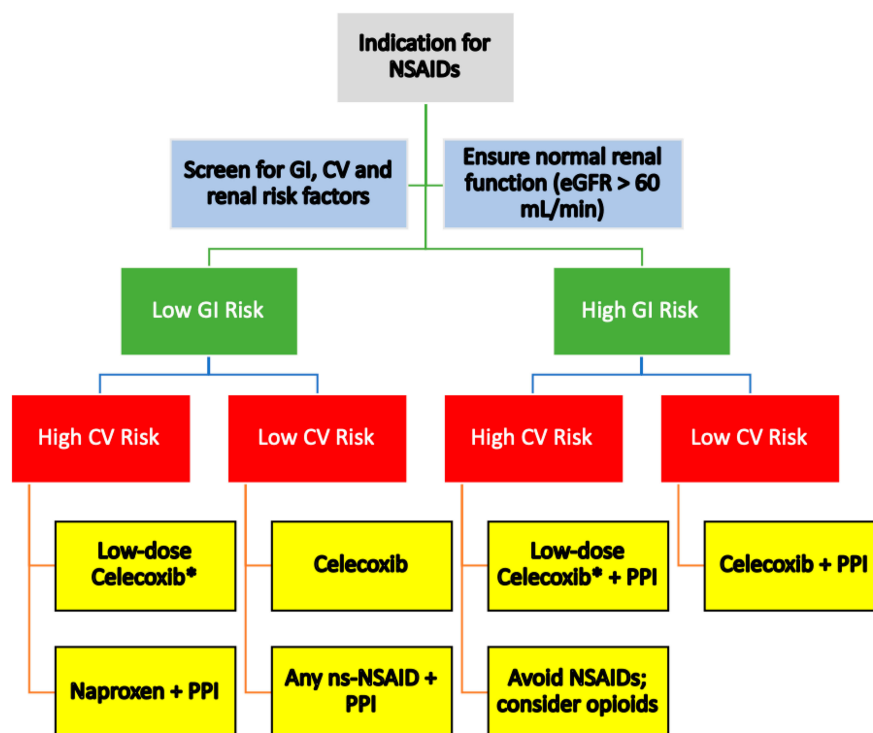


Figure 1 Treatment algorithm for choice of NSAID in patients with different risk profiles. *Low-dose celecoxib = 200 mg/day. Data from Scarpignato et al 2015, Ho et al 2018.^{31,109}

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; CV, cardiovascular; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; ns-NSAID, nonspecific NSAID.

An updated treatment algorithm is provided, which supports recommended NSAID prescribing practices based on GI, CV and renal risk factors (Figure 1).

Statement 10: Regularly monitor for drug adverse events, including high blood pressure and signs of GI bleeding. (Level of agreement: strongly agree, 79%; agree, 21%; consensus, 100%).

BP should be measured at each visit, and laboratory tests should be conducted at least once yearly to determine blood counts and renal function.

Conclusion

Inflammation is common in many chronic pain conditions where the burden of disease is high. NSAIDs are an effective therapy for such conditions, but appropriate risk evaluation is important when selecting an NSAID in order to balance efficacy and risk. This practice advisory serves to update previously published guidelines, and in particular offers PCPs a simplified approach to choosing an appropriate

NSAID for pain management based on recent evidence and according to the risk profile of individual patients. In this regard, all NSAIDs have a safety profile that requires consideration of GI, CV and renal risk. Whereas GI and CV risk were previously acknowledged according to COX-1 and COX-2 selectivity, respectively, it is apparent that this is too simplistic and appropriate risk management requires consideration of the individual (ie, non-class) effects of each NSAID. Having chosen an appropriate NSAID, there is an ongoing need for patient monitoring and risk assessment.

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